



PROFIT WINDFALL OR PATIENT WINDFALL? The Orphan Drug Act and Proposals for its Reform

Citation

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PROFIT WINDFALL OR PATIENT WINDFALL?

The Orphan Drug Act and Proposals for its Reform

'[Tihe impact on those afflicted by currently untreatable rare conditions *must* be at the forefront of our assessment. Those who wish to alter fundamentally the highly successful incentive situation of the current law should face a heavy burden in demonstrating that any proposed changes would benefit, and not undermine, the orphan drug development process.¹

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The Orphan Drug Act² is a statute with a noble purpose but a controversial history. Originally designed to spur research into drugs for conditions with extremely limited patient populations, the Act has become a highly successful means of developing new drugs for rare diseases and conditions. In total, these conditions affect a significant percentage of the population – as many as 1 out of every 13 Americans.⁴ In the ten years prior to the Act's passage, only ten drugs had been approved for these conditions, but by December 31, 1993, 569 drugs had received designation as orphan drugs under the Act; of these, over 65 had been approved.⁵ Few, then, would dispute that for its intended purpose – benefit to patients suffering from rare conditions – the Act has worked successfully.⁶

Unusually for such a popular and successful program, however, the Act has attracted frequent recommendations for change and has in fact been amended several times – in 1984,⁷ 1985,⁸ and 1988.⁹ Extensive proposals for reform were also seriously advanced in Congress in 1990 and 1992. Part of the reason for this interest stems from the statutory implication that orphan drugs are meant to be drugs of little commercial value.¹⁰

In particular, much attention on reforming the Act has arisen as a result of three instances in which high profits or high prices to consumers have led to criticism of orphan drug designations – human growth hormone (hGH), erythropoietin (EPO), and pentamidine.¹¹ Following Willie Sutton's view on banks, commentators have focused on these drugs because that is where the money is.

Approved to treat pituitary growth hormone deficiency, hGH has cost between \$10,000 and \$30,000 per year.¹² The drug has been particularly controversial because five companies have pursued hGH (and the resulting commercial potential for off-label applications is thought to belie its status as an orphan) and because of the view that the incentives of the Orphan Drug Act had nothing to do with Genentech's decision to develop hGH.¹³

EPO, which stimulates the growth of red blood cells, is approved for the treatment of end-stage renal disease but is potentially useful (and highly profitable) in treating a variety of anemias. The drug costs about \$8000 per year; most of it (about \$400 million worth) is bought by Medicare.¹⁴ The company maintains that its high price reflects its development costs.¹⁵ The drug is controversial because it was approved for anemia within a certain

discrete population ... at a time when it had already become the standard of care within another, people with

„¹⁶

AZT-induced anemia.

Pentamidine treats pneumocystis carinii pneumonia (PCP), a major complication of AIDS. After the existing manufacturing capability of the drug was destroyed, the Centers for Disease Control recruited Lyphomed -

- then a small biotechnology company - to produce the drug, after refusals from other companies.¹⁷ The drug cost about \$1000 per year in 1990.¹⁸ It has attracted great interest not only because of its AIDS-related indication but because of its high price and a controversy regarding approval of a different form of treatment.¹⁹

It is clear that Congress did not intend these and similar results when it passed the Act. But the fact remains - and this has always been the primary cause for unease about significant reform of the Act - that drugs such as pentamidine and EPO would not have been developed without the incentives of the Orphan Drug Act. These drugs frame the issues - shared exclusivity, patient cap, sales cap - that have fueled the debate over reform of the Act.

It is not the purpose of this paper to solve the problems posed by these three drugs. As of 1990, only six orphan drugs were approved for populations greater than 50,000; in 1992, of the designations 87% of the marketing are for patient populations of less than 100,000; 69% are for less than 50,000; 47% are for less than 25,000.²¹ Instead, the author's perspective is to ensure that such drugs do not act as spoilers for the incentives to achieve the purpose of the Act - to encourage research into orphan conditions. Overinclusive reform could have a significant chilling effect on research and development of orphan drugs - particularly given Congress' frequent attention to the Act, which puts drug companies in the spotlight. Proponents of extensive reform point to provisions in the Act (particularly the idea of a race to approval) in which market mechanisms act as a disincentive to research. Yet the very success of the Act belies this notion. The heavy hand of government is more likely than the invisible hand of the market to dampen research.

In 1990, there was once again a significant Congressional move to reform the Act. Notably, the proposed H.R. 4638 would have adopted a provision on 'shared exclusivity' for marketing if drugs were developed simultaneously and required companies (and FDA) to estimate the patient population for an orphan condition at a date three years after the date of designation. The bill provided for three conditions to be met for the simultaneous development that would lead to shared exclusivity: the sponsor of the second drug must request designation within six months of the publication of the initial designation, must begin human clinical trials not later

than 12 months after the initial sponsor, and must submit the application not later than 12 months after the initial sponsor. Although the bill represented a hard-fought compromise among Congress, patient advocacy groups, and industry, President Bush pocket vetoed the bill on November 8, 1990.[~]

The President's statement gave several reasons for the veto. Most important, he stated that individuals with rare diseases may suffer if the bill became law. He attributed the program's success in large measure to the provision for market exclusivity. By adopting shared exclusivity in certain circumstances and by withdrawing approval of exclusivity once a patient population exceeds 200,000, the bill would weaken incentives to develop orphan drugs. Finally, the President noted that the patient limit rule applied retroactively, which would send a troublesome signal regarding the Government's ability to change incentives unilaterally.

Since the President's veto, a number of proposals have been made to reform the Act, most importantly S.

2060, introduced by Senators Kassebaum and Metzenbaum in 1991.²³ Many of that bill's main features track H.R.

4638; the bill also introduces the concept of a sales cap. Since it is likely that any effort to reform the Act in 1994

will be patterned to some degree after S. 2060, this paper will describe the bill in some detail.²⁴

Notably, the bill extended the period of marketing exclusivity from seven to nine years and provided two years of exclusivity under all circumstances, while dropping the concept of shared exclusivity.²⁵ Companies requesting orphan drug designations were also required to make a projection as to the number of persons who will be affected by the disease or conditions three years from the date of approval. Under Section 3, once HHS determined that the cumulative net sales of a drug reached \$150 million during the period of exclusivity, HHS would begin to review any other applications pending for the designation. Once cumulative net sales reached \$200 million, exclusivity is terminated, and other applications may be approved.

S. 2060, then, is a radical attempt to refocus the Act on true orphan drugs for rare diseases and to use the threatened loss of exclusivity to limit prices for orphan drugs. The question, however, is whether this attempt is so overinclusive that it weakens the incentives for companies to develop orphan drugs. The author believes that the bill, however well intentioned, goes too far. This paper will analyze each proposed reform (and a few ideas not formally part of the bill) with a view to predicting its practical effect if a similar bill became law. On the (perhaps wishful) assumption that recent press reports accurately reflect the 1994 bill, that will be examined as well.

Reportedly, the new Metzenbaum-Kassebaum bill will reduce the period of exclusivity to four years, with an extension to seven years if total sales have not exceeded \$200 million in the four-year period. Marketing exclusivity would end once a condition has more than 200,000 people; the bill also restores the concept of shared exclusivity as in H.R. 4638.²⁶

Exclusivity

Virtually all commentators believe that marketing exclusivity is the crux of the Act.²⁷ As Commissioner Kessler testified in 1992, [a]ny weakening of the exclusivity provisions almost certainly will discourage development of orphan drugs in the future. This point cannot be emphasized strongly enough.²⁸ In fact, the National Commission on Orphan Diseases recommended in 1989 that the seven-year period of exclusivity be increased, and Senator Hatch reportedly favored in 1992 a program for nine years' exclusivity for drugs with very small patient populations.²⁹ The 1993 proposal of the Biotechnology Industry Association reportedly reduced exclusivity from seven to five years but also provided for a five-year extension if the patient population was under 100,000.~ Practically, this would extend exclusivity to 10 years for most orphan drugs.

Yet critics argue that [i]t is difficult to call something an orphan when two or more entities want to be the parent.³¹ So during debate on H.R. 4638, Representative Bliley defended shared exclusivity as based on fairness for companies that truly develop the same drug simultaneously.³² On the other hand, while few orphan drugs -indeed, this would likely apply only to the most profitable - would be subject to (forced) shared exclusivity, a company would theoretically have to consider losing 50 percent of the market.~ And opponents argued that a deal is a deal... . you can't change the rules in the middle of the game.~ For these reasons, as late as February 1990, the National Organization for Rare Diseases opposed shared exclusivity in any shape or form.³⁵

It is far from clear that a duopoly would lower price. Not only do companies have a need to recover their costs, but, as the case of r-hGH shows, competition among two exclusive suppliers has not lowered price.~ In fact, total costs may well rise because both companies will maintain competing marketing efforts. This effect would only be magnified by extending the period of exclusivity for products where exclusivity is shared. Some would respond that lengthening the period gives companies a chance to spread out costs over a longer period (thus

lowering the initial price), but companies need to generate money for future R&D as well as maximize profit.

Given this, from the perspective of patients, there is little benefit from reforming the provisions on exclusivity, and the dangers of doing so are potentially great. Under the regulations implementing the Act, FDA may revoke market exclusivity if the holder cannot assure the availability of adequate supplies of the drug.³⁷ This

– perhaps combined with a mandatory giveaway program discussed *infra* – should be the limit of tampering with exclusivity. That having been said, the 1994 Kassebaum-Metzenbaum proposal (though without shared exclusivity) is the best attempt made so far, precisely because it provides for an automatic extension of exclusivity to the current seven years for most orphan drugs.

Shared exclusivity is already permitted – even encouraged – on a voluntary basis;~ the case for making it mandatory is simply not proven. Tempting as it is to seek to prevent abuses of exclusivity, if we accept the testimony of one interested observer, new designations for 1991 – the year after the controversy over H.R. 4638 – dropped by 25 percent.³⁹

Patient Cap

Current law requires that an orphan drug not be designated if the total population affected by the condition exceeds 200,000. Yet this limit applies to each indication, not the total population which could benefit from the drug. Some commentators therefore have argued for a patient cap, particularly given the rapid spread of AIDS above the 200,000 level. This could be accomplished by requiring withdrawal of exclusivity once the patient population rises above 200,000 or, alternatively, by requiring FDA before designation to estimate the patient population three years after designation.

It is frankly difficult to see how this would work in practice. FDA hardly has the resources to monitor this, save in extreme cases such as AIDS. Reliable data on patient populations is hard to find, especially concerning patients not currently under treatment.⁴¹ The cap would act as a positive deterrent for diseases with populations near the patient cap (multiple sclerosis is perhaps the best example); if the scientific or clinical definition of the disease changed, a company could lose exclusivity. Proponents would retort that any drug in this category is not a true orphan and thus does not deserve the benefits of the Act. The revision of the definition of a rare disease

to a 200,000 patient standard has lasted for nearly a decade. Very clearly, certain patient groups believe they are within the statute's scope; it would be cruel to remove them.

Beyond this, a patient cap raises many other practical questions: Would the 200,000 patient limit be breached through off-label uses?⁴² Should a company be forced to keep records of the number of patients using an orphan drug? What about patients who (for whatever reason) are not prescribed the drug but prefer other forms of therapy? Would FDA just react to a citizen's petition from a competitor alleging breach of the limit? Such a petition would engender protracted administrative litigation and waste FDA resources. In any event, unless the date is within one year of the end of exclusivity, FDA will not likely have begun approval of a competitor's NDA. Thus exclusivity would de facto continue at least for a time.

The special case of AIDS in fact argues against imposing a patient cap. As Acting Commissioner Benson noted, [e]arly in the AIDS epidemic, it was very difficult to find any manufacturers willing to invest in products for the disease, and the Orphan Drug Act provided an important incentive at that time.⁴³ Not only did the actual number of AIDS patients grow, but the definition of AIDS itself changed over time – and with a patient cap, the resulting uncertainty would have been a disincentive for companies to invest in research.

It is doubtful there will be another crisis similar to AIDS, but even if there is, the Act would provide crucial incentives at the beginning of the epidemic. If there must be some form of patient cap, by far the best would be simply to amend 21 CFR §316.29(c) and give FDA discretion to withdraw designation in the case of sharply exploding population. Only FDA can make the necessarily individualized determination whether the rise in patient population combined with the availability of alternative drugs would justify revoking exclusivity.

If the social goal of the Act is to pursue the drug to its greatest public good,⁴⁵ then a patient cap counters that goal. This is particularly true for drugs developed using biotechnology, for the Act (in practice) often substitutes as a surrogate for patent protection⁴⁶; a cap could thus prevent full exploitation during the period necessary to recoup the costs of research.

Sales Cap/Recoupment Cap

The idea of a \$200 million sales cap seems to have originated in an extrapolation from FDA's regulations on generic drugs, under which a blockbuster drug is defined as one whose sales exceed \$50 million per year.⁴⁷ Of all the proposed reforms to the statute, this – perhaps even more than exclusivity reform – is the most troubling.

Development of drugs is expensive. The price we as a nation pay for a quality drug approval system that only permits marketing of demonstrably safe and effective drugs is extraordinarily high developmental costs. The process is fraught with uncertainty, which only heightens the expense.

The situation of each drug – its development costs, its use, and its expected population – is different. Yet a cap is arbitrary. It ignores the potential of chronic use; many of the most innovative orphan drugs must be taken for long periods of time. Defenders of the proposal would undoubtedly argue that chronic use implies greater profitability. But this would in effect discriminate between types of orphan drugs, to the detriment of patients' wellbeing. For companies – and for FDA regulators – the cap would be a serious administrative burden.⁴⁹ Over time, the cap will almost certainly discourage orphan drug research: the figure of \$200 million would stay in the statute, while the cost of R&D constantly increases. As with the patient cap idea, it is unclear whether off-label use should be included in a sales cap – 5. 2060 refers to a drug, not an indication – particularly if the manufacturer diligently discourages off-label use. Even if it is true, as proponents claim, that 97 percent of orphan drugs can never expect to realize sales approaching \$200 million,⁵⁰ the cap would disproportionately impact pharmaceutical, as opposed to biotechnology, companies. As one biotechnology leader has said: there's no \$200 million biotech drug out there.⁵¹

Some advocates favor the sales cap simply as a way of encouraging lower prices.⁵² While the argument might have some validity if the sales cap were calculated on an annual basis, it is simply wrong for cumulative sales. A drug company must recoup its costs of development. There are basically three ways to do so: sale of the drug, government grants for development, and extension of the tax credit. (The fourth, cross-subsidization of orphan drugs by other drugs, is called into question by the cap.) The third would cost the government revenue, and the second entails more government spending (precisely the problem complained of in the case of EPO). Even Jean McGuire of the AIDS Action Council admitted that it is not certain that prices for AIDS drugs would be lower

if they were outside the Act. Wax 63. This view was supported by a San Francisco group called Direct Action for Treatment Access, which called the idea impossible. ... A drug that gets approval has to pull far more than its own weight.~ In any event, the cap could also have a deleterious effect on manufacturer drug giveaway programs.

Finally, the bill's definition of cumulative net sales is unsatisfying. Arguably, to reflect the true social benefits and costs, the figure of savings in government health programs should be included.~ Given the highly varied situations from drug to drug, if Congress insisted on some form of a sales cap, it would seem better to proceed by FDA rulemaking than by detailed statutory formulas.

Consideration of Orphan Drug Issues Within HHS

H.R. 4638 and S. 2060 would have established within HHS an Office for Orphan Diseases and Conditions at a level within the Department with sufficient authority to assure full implementation of [its] functions and

responsibilities. This Office would replace the Orphan Products Board established under the 1983 Act. HHS strongly continues to oppose the provision as a weakening of FDA control over implementation of the Act and an intrusive effort to manage orphan product development. Commissioner Kessler has termed the provision unnecessary and redundant.⁵⁵ By contrast, some rare disease advocates strongly support it.~

Some have asserted that this provision was the real reason for the veto of H.R. 4638.~~ Irrespectively, one should examine what effect it would have on the operation of the Act within I-HS and FDA. From the perspective of agency management, perhaps the most objectionable feature of the section is the proposed advisory committee. The committee, appointed by the Secretary, would consist of five representatives of organizations of persons with rare diseases, three research scientists, and three representatives of health-related companies.~ Its duties are extremely broad: to advise the Office in carrying out the fun~tions of the Office under this section. The committee would, in short, have a continuing role, which could easily become a serious intrusion into agency management, both in the operation of the orphan drug program itself and in terms of the priority given orphan drugs within FDA and HHS. The committee was quite directly intended to be a strong advocate for devoting increasing amounts of FDA resources to orphan drug concerns.

It seems difficult to believe that such a committee is really necessary. The success of the Act, as attested

by the number of orphan drug designations, shows that industry is mindful of the advantages the Act offers. A perceived need for better coordination between relevant agencies can be met without shifting the center of gravity in orphan drugs towards the committee. HHS should simply ensure that individuals from all relevant agencies serve actively on a revitalized Board.

Where the committee could have its most serious – and potentially deleterious – effect is in the targeting of research towards conditions which have not yet benefitted from the Act. While government has a legitimate role in calling attention to conditions which would benefit from more intensive research, it is easy to imagine that the process might result in the government attempting to find a company to undertake research. It is at best unclear that government is capable of making such a determination – the effects of which, for good or ill, would be magnified greatly by the provision for seven-year exclusivity.⁵⁹ FDA’s opinion is similar: Government is ill-equipped to do that kind of a job.⁶⁰

Windfall Profits Tax

Representative Fortney H. (Pete) Stark has twice introduced bills to enact a windfall profits tax for orphan drugs which are excessively profitable.⁶¹ The 75 percent tax would apply once a company has recouped development costs; companies would be allowed only a 25% profit over the yearly cost of production and marketing.⁶²

The advantage of the approach is that it would avoid any detriment to the exclusive marketing provisions of the Act. Yet notably absent from the Stark bills is any rollback provision, either for new drug research generally or for orphan drug research in particular. The proposition is more defensible if the companies concerned truly are earning windfall profits from an activity justified by its social rather than its commercial utility. Since the purpose of the Act is to encourage development of orphan drugs, that purpose is furthered if companies are encouraged to plow their profits back into development of other orphan drugs. (This would presumably reduce the need for Federal funding of orphan drug research as well.)

Instead, Stark’s bills, particularly the second, are baldly anti-competitive and would reduce efforts into research on orphan drugs. Corporate social responsibility cannot simply be enacted by statute. The tax would

operate precisely opposite to the purposes of the Act and the choices Congress made in enacting it.

Stark's bill does, however, include pre-clinical development costs (less the amount of Federal funds used for development) as part of the calculation as to when the windfall begins. The tax would be far more palatable if it were combined with an extension of the tax credit to include pre-clinical research. Alternatively, the tax credit could be made refundable, to ensure that the tax does not act as a disincentive to research.

'Salami Slicing and the Definition of Clinical Superiority

Many critics have noted that the Act functions as an invitation to scope out a narrower group than may otherwise benefit from the treatment to gain the incentive of marketing exclusivity. This salami slicing has the potential to be a serious problem, although the record of designations shows that the facts do not show an exclusive pattern. Thus, for instance, Botulinum Toxin Type A has received six orphan designations, held by three different companies.⁶⁵ On the other hand, one company (Hoffmann-La Roche) holds seven designations (but only one approval) for recombinant interferon γ -2A, and Biogen holds six of seven designations for recombinant interferon γ .⁶⁶ While this raises the prospect that one company may corner the market, it does at least reward the company which exhaustively researches a drug's potential uses before seeking FDA approval.

FDA's new regulations and participation in the drug approval process help to guard against salami-slicing and should preclude any related changes to the Act. The Centers for Drugs and Biologics have a role in determining whether a proposed study is appropriate or whether the indication should be widened.⁶⁷ Broadly, FDA's standard is that the proposed indication must not be an obvious manipulation of the law to attempt to obtain approval for a minor indication when it is clear that the intended use is for a much broader indication.

The controversies over aerosolized pentamidine and hGl-I raised the question of whether FDA should approve new orphan drugs if they are chemically different in any way or whether there must be a showing of clinical superiority.

FDA has decided strongly in favor of a standard of clinical superiority, determined by greater effectiveness, greater safety in a substantial portion of the target populations, or, in unusual cases where the drug makes a major contribution to patient care.⁶⁹ Thus a later recombinant version of a drug may be approved as well as the

natural product because safety is enhanced, even if the dosage remains the same.

The third category is intended to be narrow,⁷¹ and it quite deliberately gives FDA discretion to proceed on an individualized basis. (Cost, however, is not of itself a factor.) This kind of discretion in FDA might well have resolved the situation of aerosolized pentamidine. Admittedly FDA is not qualified to make an economic judgment on a drug, but it is able to make a therapeutic judgment.⁷²

More directly, the standard of clinical superiority accords with the statute's emphasis on marketing exclusivity. Given the strong incentive of marketing exclusivity, it seems obvious that a company would, rather than simply sleeping on its rights, want to seek to develop better forms of the drug, including easier forms of administration. The alternative – approval of a designation if a second drug is structurally different⁷³ – would virtually undermine marketing exclusivity – it is too easy, in the case of a highly profitable drug such as hGH, simply to construct a chemically different version of the drug. Proponents respond that for a true orphan drug of limited commercial value,⁷⁴ no company would spend a lot of money and devote precious resources on the development of a second NDA.⁷⁴ In the author's view, this too casually ignores the progress of science – if a drug is found to be useful for additional indications (not all of which can be predicted before approval), a company may well have the incentive to undertake additional research and should have the ability to benefit from its discovery if it is in fact the first to be approved for the additional indication.

Mandatory Giveaway Programs

In 1992, Senators Hatch and Thurmond reportedly proposed that firms which have received orphan drug approvals develop a mandatory access program⁷⁵ to ensure availability of orphan drugs to those who cannot afford them. The 1992 hearings on proposed reforms to the Act focused attention on access to drug giveaway programs. Partly in response to this, other efforts are being made to expand access to these programs; both the Pharmaceutical Manufacturing Association and Senator Pryor's Aging Committee have prepared directories of the programs.⁷⁶ Yet the supporters of 5. 2060 were skeptical that giveaway programs would work in practice, for fear that other patients would pay higher rates for the drug and needy patients would not receive information about the programs.⁷⁷

Giveaway programs are not a complete solution, and mandating giveaways might have some disincentive for production. But the discouraging effect would seem to be less than if Congress were to take other actions such as reducing exclusivity or proposing a sales cap. A sales cap might well increase the level of drugs given away. FDA could effectively do the same thing by requiring longer clinical trials before an orphan drug is approved; in the trials, the cost to patients is sharply regulated.

Liability Reform

The potential for liability may act as a disincentive to development of orphan drugs, since the smaller population precludes companies from spreading out the costs of liability risks over a large patient population. This problem, however, was not addressed in S. 2060 or similar bills. One idea proposed is to have a 1% fund from the sale of orphan drugs, similar to that for childhood vaccines, in exchange for a liability waiver.⁷⁸

Separate Treatment for AIDS and Other Conditions

Some commentators have simply proposed removing all AIDS-related drugs out of the Orphan Drug Act,

because of the large AIDS population and fears regarding marketing exclusivity and price.⁷⁹ Regardless, the

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development of drugs for AIDS which receive orphan status continues. While AIDS itself is no longer a

legitimate orphan designation,⁸¹ opportunistic infections with smaller patient populations continue to be covered. It is important to remember that the Act played a crucial role in the early development of treatments for AIDS, including AZT, designated in 1985 and, in 1987, the twenty-first orphan drug to receive marketing approval.[~]

AIDS is of course a serious public health crisis which deserves national attention. But it would be contrary to the purpose of the Act to have considerations relating to AIDS drugs in effect swallow the other diseases which fall under the concern of the Act. To that extent, a separate national policy for AIDS – guided by a separate statutory structure – should be seriously considered. More generally (and more easily), one should simply amend the Act to require that any disease defined as an epidemic of large proportions by the Centers for Disease Control is not an orphan disease.⁸³ But this poses the danger, as Ms. Meyers admitted, that biotechnology companies would decline to perform AIDS research because of uncertainty over patent rights.

Similarly, some advocates have proposed special legislation for dedesignating orphan drugs (such as hGH) which have seen extraordinary profitability. This accords with the recommendation of the Chair of the National Commission on Orphan Diseases for surgical action by Congress to correct specific abuses⁸⁵ and would send a strong signal that abuses under the Act will not be tolerated. It would also avoid potentially harmful tinkering with the Act's basic structure. But separate legislation can be time-consuming and difficult to enact.

Conclusion

The question, then, becomes a difficult balance. All sides recognize that the Act's structure of incentives has provided tremendous impetus for the development of orphan drugs, yet all equally recognize that there have been abuses. Unquestionably the Act – particularly counting its abuse – has cost the Federal Government significant resources.

Does this make sense? Very clearly it does on the moral plane.⁸⁵ On the scientific level, the question then becomes whether research and development of drugs generally is furthered by development of orphan drugs –whether learning more about rare diseases translates into more understanding of common ones.

Many drug and biotechnology companies, as evidenced by their behavior under the Act, would argue that

the proposition is sensible. Assuming this is correct, then, in contrast to the views of some in Congress, the author

does not view profit per se as the problem. As one developer of orphan drugs has written, it is important to judge

a new orphan candidate at the time the research is started, and not after the pioneer has proved to the world that

a wonderful new miracle drug has been discovered.⁸⁷

If, as in the case of Lyphomed and pentamidine, a company is able to use an orphan designation – by definition, research that few are willing to carry out – to ensure its corporate future (and help raise capital for future drug development), it seems unfair to deny that possibility. Companies feel free to reinvest in new drug development because the Act's incentives provide economic certainty.⁸⁸ This is particularly true for new biotech companies that may only have one product on the market. Are they not permitted to make some return on investment, if only to invest in new drug development? Again, that is a social and economic choice Congress made when it enacted the Act.

Even despite the abuses under the Act, there is also a question of fundamental fairness, of the behavior of government towards those it regulates and taxes. People who invested in orphan product development with the promise of market exclusivity should not be punished for taking the Federal Government at its word.~ In short, do the abuses justify retroactively reducing incentives for orphan drug development for all companies?

One solution seems clear: to reinforce discretion in FDA, as the final regulations do for issues such as the definition of clinical superiority and appropriate patient populations. An overriding image in food and drug law is to view the FDA as Gulliver in Lilliput – sought to be restrained by a multitude of tiny bonds, he nevertheless breaks free. Here, though, FDA discretion is both appropriate and expected by the statute. Significantly, the National Commission on Orphan Diseases recommended that abuses be handled individually, not make systemic changes to the Act.⁹⁰ This advice, if followed, virtually demands wide FDA jurisdiction to make changes in the Act's operation; Congressional action is simply too slow to correct most abuses and frequently cuts with too wide a scythe.

Yet FDA cannot solve one outstanding problem with the Act, price. It is not an economic agency. One can be deeply moved, even angered, by the serious plight of those who cannot afford orphan drugs and yet reluctantly conclude that no major changes should be made in the Act. Without the Act's incentives, how would the drugs have even come to market? Without the company making something of a profit, how can it afford drug giveaway programs? Price is simply not in FDA's jurisdiction.

FDA can, however, focus debate on the medical analysis of the real costs of drugs: If an orphan product is a substitute for lengthy, expensive hospital care that runs hundreds of thousands of dollars per year, or a costly surgical procedure, what is the appropriate charge [?J~' And the fact remains that most orphan drugs are approved for conditions with very small patient populations or small occurrences, such as various toxicologies.

Is it good public policy to drive an overhaul~ of the Act based on a handful of controversial drugs out of over nearly 600 designated? To answer that, one must decide what is the public policy behind the Act. If the purpose of the Act is to encourage research into drugs for rare diseases, then the Act should not be tinkered with. One must consider the real cost of therapy – including the current alternatives of different or no therapy. Any full accounting of the benefits and costs of the Act must also include savings to patients and insurersY³ By this

measure, significant reform of the Orphan Drug Act deserves the Scotch 'verdict of not proven.

The granting or repeal of economic incentives is a social choice. Congress made a clear choice in 1983 to encourage research and development of drugs to treat rare diseases. It set the incentives high enough to be attractive to major drug companies. It understood that there might well be abuses of the Act⁴. Had Congress simply wanted to provide a break even amount, it could have done so. The Act's work is not done. Drugs are still needed for many orphan diseases including narcolepsy, multiple sclerosis, and many others. The implicit bargain of the 1983 Act was market exclusivity – and the potential for windfall – in exchange for the expensive research. To change the bargain now – and run the risk of jeopardizing the Act's success in treating those who suffer from rare diseases – is like penalizing Sutter for finding gold in California.

ENDNOTES

1. 5. REP. No. 102-358, 102d Cong., 2d Sess. (1992) at 16 (minority views of Senators Hatch, Thurmond, Durenberger, and Cochran).

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2. Pub. L. No. 97-414, 96 Stat. 2049 (1982). The general provisions of the Act have been well described in several scholarly articles. See, e.g., Carolyn H. Asbury, The Orphan Drug Act: The First 7 Years, 265 3. AM. MED. ASS'N. 893-897 (1991); Marlene E. Haffner, Orphan Products: Origins. Progress, and Prospects, 31

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Act: Is Resolution on the Way?, 46 FooD DRUG COSM. L. J., 327 (19~1); Li-Hsien Rin-Laures and Diane

Janofsky, Note, Recent Developments Concerning the Orphan Drug Act, 4 HARV. 3. LAW AND TEc. 269 (1991).

3. Author's conversation with Peter Barton Hutt, January 22, 1994. See also H. REP. No. 100-473, 100th Cong.

2d Sess. (1988) at 4: Orphan drugs are drugs expected to be, at best, only marginally profitable due to the small patient population that will use the drug [but which arej developed nevertheless as a public service.

4. See CHICAGO SUN-TIMEs, Dec. 7, 1993, at 6.

5. See 138 CoNG. REC. H11931 (daily ed., Oct. 23, 1990) (statement of Rep. Scheuer) (data for 1973-1982). Of the 549 products which had received orphan designation as of December 31, 1993, 359 are drugs and 190 are biologics. Telephone conversation with FDA Office of Orphan Products Development, January 11, 1994. Some drugs have been approved for more than one indication; as of December 31, 1993, 90 drug designations had received marketing approval. Cumulative List of Orphan Product Designations and Approvals (On file with FDA Office of Orphan Products Development).

6. It is important to remember that the purpose of the act was to encourage pharmaceutical companies to develop drugs for rare diseases, and it has done just that. That is the most important thing to remember. Orphan Drug Act: Hearing before the Subcommittee the House Committee on Energy and Commerce, 101st Cong., 2d Sess. (1990) at 29 (statement of Abbey S. Meyers) [hereinafter ODA Hearingi].

At least one other major pharmaceutical producing nation - Japan - has recently adopted a similar

statute. The amendments to the Pharmaceutical Affairs Law, which went into force on November 1, 1993,

provide a program for development of orphan drugs. The population ceiling for

incidence of a rare disease or condition is 50,000. See MARKERLEITER, Nov. 29, 1993. In 1993, the first year of the law, there were 200 applications for orphan drug status, leading to 70 designations. Nineteen drugs were given subsidies. In 1994, total subsidies will amount to ~¥400 million (approximately US \$3.8 million). See BIOTECH AND MEDICAL TECHNOLOGY, Jan. 6, 1994, summarizing an article in NIKKAN KOGYO SHIMBUN, January 1, 1994, at 22.

In terms of the United States population, the Japanese population ceiling would translate into a ceiling of approximately 125,000 people. (Alternatively, the Japanese figure would be 80,000 if the American standard of 200,000 were used.)

The European Community and its Member States do provide grants for research into new drug development, but there is as yet no similar orphan drug program in the Community.

7. Health Promotion and Disease Prevention Amendments, Pub. L. No. 98-551, 98 Stat. 2817 (1984). This bill changed the definition of a rare disease from one of profitability on the drug approved for the indication to one of a patient ceiling of 200,000.

By setting a standard and not forcing companies to undertake the difficult task of evaluating profitability prospectively, the Amendments encouraged orphan drug research.

8. Orphan Drug Amendments of 1985, Pub. L. No. 99-91, 99 Stat. 387 (1985). This bill extended the Act's protections to drugs which could be patented as well as to unpatented drugs. While many drugs (including AZT) early considered to be likely candidates for orphan designation were unpatentable, this Act served to spur orphan drug research.

9. Orphan Drug Amendments of 1988, Pub. L. No. 100-290, 102 Stat. 90 (1988). The Amendments contained two major provisions: they expanded eligibility for clinical grants to include orphan medical foods and medical devices and they required a company proposing to cease production of an orphan drug to notify FDA one year before the proposed cessation. Companies were also specifically prohibited from submitting a paper NDA for approval of their drug for a different orphan indication.

Representative Waxman had tried earlier in the year to revise the Act to modify its provisions on exclusivity substantially. See 46 CONG. Q. WKLY. REP. 686 (Mar. 12, 1988). The attempt failed in the full House Energy and Commerce Committee, and the bill as enacted was substituted.

10. 5. REP. NO. 102-358, 102d Cong., 2d Sess. (1992) at 2.

11. Space precludes an extensive discussion of these drugs here. For more detailed information on these drugs

and the controversy surrounding them, see generally Carolyn H. Asbury, The Orphan Drug Act; The First 7

Years, 265 J. AM. MED. ASS'N. 893-897 (1991) and Stephen E. Lawton, Controversy Under the Orphan Dr

Act: Is Resolution on the Way?, 46 FOOD DRUG COSM. L. J., 327 (1991). The Congressional hearings on the

Act in 1990 and 1992 also focused primarily on these drugs.

A few other orphan drugs – notably Ceredase[®] approved for the treatment of Gaucher disease – have attracted sharp attention in recent years, often because of the price of the product. ~ Anticompetitive Abuses of the Orphan Drug Act: Invitation to High Prices: Her
Antitrust, Monopolies, and Business Rights, 102d Cong., 2d Sess. (1992) [hereinafter Anticompetitive Abuses]. Id. at 5 provides a list of these blockbuster drugs.

12. ODA Hearing at 1 (figures). Genentech developed a recombinant product (r-hGH) which had 192 amino acids rather than 191 in the natural product. The recombinant product also is safer. The Act effectively did not apply to hGH until 1985, because patentable. Id. at 78 (statement of Thomas S. Wiggins).

13. Id. at 32 (statement of Abbey S. Meyers). Genentech, the holder of exclusivity for the orphan indication for hGH, strongly denies the charge, maintaining that the company pled this in the alternative in Federal court. The

president of a competing company stated the prevailing view that the situation with uGH was not at all what Congress had in mind when it passed the Orphan Drug Act. 14. at 71 (statement of Thomas S. Wiggans).

Genentech's significant sales are expected to continue through 1994, even though Protopin® loses its marketing exclusivity in March. In 1993, sales of the drug amounted to about \$215 million; in 1994, the figure is expected to be \$195 million. See Genentech Says Earnings Estimate Reasonable, REUTERS, Jan. 10, 1994.

14. ODA Hearing at 2 (statement of Rep. Waxman) (yearly cost); F-D-C REPORTS, THE PINK SHEET, Dec. 2, 1991, T&G-12-13 (Medicare payment).

15. Amgen has operated with a net deficit since we began 9 years ago. Even today we still are in the red, which means we haven't paid back what we owe, not to speak of a return on investment, and we have had investments of over \$350 million in all. ODA Hearing at 197 (statement of George Rathman).

16. id. at 47 (statement of Jean McGuire).

17. See generally Therapeutic Drugs for AIDS: Development, Testing, and Availability Before 100th Cong., 2d Sess., (1988), at 413ff. (testimony of Brian Tambi, Vice President for Corporate Development at Lyphomed). Ironically, in light of later developments, the National Organization for Rare Diseases gave Lyphomed an award in 1987, noting that it has been an outstanding model for the pharmaceutical industry as a developer of orphan drugs. id. at 415. The letter inviting Lyphomed to accept the award is even more blunt: the company deserved the honor particularly, because you were willing to adopt pentamidine at a time when no one was able to predict the scope of the AIDS epidemic. Id. at 425, Letter from Abbey Meyers to Lyphomed, December 1, 1987.

18. ODA Hearing at 2 (statement of Rep. Waxman).

19. Lyphomed's product was administered in clinics. Fisons then developed an aerosolized form of pentamidine and sought approval from FDA. The issue of price became a major source of controversy between Lyphomed and Fisons. Among the uncontroverted facts: Lyphomed's original price in 1984 was \$24.95 per unit. Therapeutic Drugs, supra note 17, at 416. It then hired a sales team to cover the major AIDS treatment hospitals, id. at 417, and inform them of pentamidine's availability and use. By 1988, the cost of the drug had risen to \$99.45 per vial, but Lyphomed provided it free to 3000 patients (70,000 vials per year).

Lyphomed argued that the drug should be allowed to bear itself the costs of development and that the \$20m for trials essentially equal[led] the company's net profit for 1987. Id. It further argued that now that the product had achieved commercial viability, a major company has developed a sudden interest and sought

to win approval for its version of the drug.

At this point the controversy – and the implications for the Act – become much thicker. Fisons received orphan drug designation (not approval) for its pentamidine product for the prevention of PCP. Lyphomed (incorrectly, in the author's view) asserted that this was an abuse of the Act because Lyphomed was at the same time seeking designation for its product for a prevention indication (as opposed to its current treatment indication) as well. Id. at 427.

Congress clearly had some concerns about Lyphomed's use of its exclusivity. Representative Weiss wondered why the company had to maintain 27 people on its sales force at over \$100,000 per year to sell one product, virtually accusing the company of using the exclusivity provision to seize the opportunity to grow at the expense of AIDS patients. Tambi responded that other companies had already turned down CDC's invitation, and that it required a physician sales force to market a drug to physicians. Id. at ~1-42.

See generally 181-183 for Lyphomed's version of the comparison. 187-191 for Fisons'. See also Anticompetitive Abuses at 97 (European price \$25 in

1992). Lyphomed was later purchased by the Fujisawa pharmaceutical concern.

20. ODA Hearing at 32 (statement of Abbey S. Meyers).

21. Id. at 1 (approval); Marlene E. Haffner, Orphan Drugs: Where Have We Been Since AZT?, unpublished speech, May 28, 1992 at 15 (designations).

22. The President issued a Memorandum of Disapproval. See 1991 (II) PUB. PAPERS OF THE PRESIDENT's 1587-

88. The difference between this document and a veto message is that in a pocket veto, there is no requirement that the President state his objections to the bill (or even write anything at all) in a memorandum to the

originating House. See U.S. CONST. art. I, § 7, cl. 2. There is no reference in the Memorandum to the Office of Orphan Diseases and Conditions (which arguably would otherwise have been required).

Some commentators have suggested that the veto was a surprise. *See infra* note 57. Yet on June 20, 1990, Secretary Sullivan wrote to Representative Waxman that [d]espite concerns about anomalies in the operation of the act, we have concluded that the act should not be altered in any fundamental manner. True, this did not amount to a formal Statement of Administration Policy as is usually sent to Congress to threaten a Presidential veto, and without such a Statement, the Administration usually recommended signature on any eventual bill as a matter of good faith with Congress. But Congress can hardly have been unaware of the Administration's views, and on September 29, Congressional Quarterly Weekly Report reporter Julie Rovner -

- who had closely followed the bill all year - wrote that its fate is uncertain. 48 CONG. 0. WKLY REP. 3133. (Sept. 29, 1990).

23. 5. 2060, Orphan Drug Amendments of 1991, 102d Cong., 1st Sess. (1991) (introduced Nov. 26, 1991, reported with an amendment Aug. 6, 1992). Senators Kennedy and Inouye later joined as cosponsors. The bill was reported by the Senate Labor and Human Resources Committee but failed to win passage on the floor.

A companion bill in the House was H.R. 4959, Orphan Drug Amendments of 1992, 102nd Cong., 2d Sess. (1992), introduced by Representatives Studds and Waxman on April 9, 1992.

24. Reportedly, the new Kassebaum-Metzenbaum bill includes provisions for shared exclusivity but, unlike S.

2060, no grandfather clause. The current draft (not yet introduced in Congress) will reduce the period of exclusivity from 7 to 4 years but provide for a three-year extension if net cumulative sales of a drug do not exceed \$200 million during the first four years. See F-D-C REPORTS, THE PINK SHEET, T&G 1-2, Dec. 20, 1993. The bill defines net cumulative sales as total U.S. sales minus discounts, allowances, and returns. See F-D-C REPORTS, THE PINK SHEET, T&G 4-5, Dec. 6, 1993. Presumably the value of drugs distributed through giveaway programs would be included in the definition of discounts, but this is unclear from published reports.

25. To address the Bush Administration's concern regarding retroactive application of any amendments, the bill contained special provisions for drugs currently on the market - a period of five years' exclusivity before the sales trigger would be applied. Drugs nearing FDA approval would basically receive four years of exclusivity. See S. REP. No. 102-358, 102d Cong., 2d Sess. (1992).

26. 48 HEALTH LEGISLATION AND REGULATION, No. 19, Dec. 8, 1993.

27. [M]arketing exclusivity by far is the chief incentive to the development of orphan drugs. ODA Hearing at 13 (statement of Dr. James S. Benson). Exclusivity is the prime incentive of the act. We do not want it tampered with. Id. at 30 (statement of Abbey S. Meyers).

28. Testimony of David A. Kessler, M.D. before the Committee on Labor and Human Resources, U.S. Senate, March 3, 1992 (hearings on 5. 2060), at 5.
29. ODA Hearing at 3 (statement of Rep. Scheuer); F-D-C REPORTS, THE PINK SHEET, T&G-8, June 15, 1992.
30. F-D-C REPORTS, THE PINK SHEET, T&G 4-5, June 28, 1993. The hO proposal also includes four years of market exclusivity under all circumstances for biotechnology-derived orphan drugs.
31. ODA Hearing at 45 (statement of Jean McGuire).
32. 48 CONG. 0. WKLY. REV. 2327 (Jul. 21, 1990).
33. Jeffrey C. Warren of the Pharmaceutical Manufacturers Association, quoted in 48 CONG. 0. WKLY. REV. 3878 (Nov. 17, 1990).

34. ODA Hearing at 4 (statement of Rep. Nielson). See also id. at 17 (statement of Rep. Bliley): To me, they all went into this knowing that the first one that comes out with it is the one that is going to get it. So, like any contest, there are winners and losers.

35. Id. at 30 (statement of Abbey S. Meyers). See also id. at 33: We are unwilling to sacrifice the fate of 20 million Americans with orphan diseases because AIDS patients want less expensive drugs. We also point out that Genentech and Eli Lilly both manufacture Human Growth Hormone and this competition has not reduced the price of hGH one cent!

36. Id.

37. 21 CFR §316.36 (1993).

38. We would ask industry to follow the example of numerous companies and share exclusivity voluntarily with competitors before an orphan drug is approved for marketing. If these drugs can be kept out of court and the visibility of lobbyists reduced on Capitol Hill, Congress may not be able to interpret some of these situations as abuses, and the money saved might benefit consumers through more affordable orphan drug prices. Use patent laws instead. Abbey S. Meyers, The Impact of Orphan Drug Regulation on Patients and Availability, 47 FOOD DRUG COSM. L. J. 9, 12-13 (1992).

In fact, two companies agreed to share exclusivity for L-Caritine. See H. REP. No. 100-473, 100th Cong., 2d Sess. (1988) at 6.

39. Anticompetitive Abuses at 140 (statement of Robert K. Dresing of the Cystic Fibrosis Association). Dresing argued strongly in favor of retaining the Act's incentives. Without data on the length of time between request for designations and the status being granted, however, it is unclear to what extent the controversy was responsible for the drop. It could well be that as the recession was beginning, companies dropped orphan drug research quickly because it seemed to afford less profitability.

40. Explicitly not permitted under current regulations see 21 CFR §316.29(c).

41. Telephone conversation with Robert Steeves, FDA Office of Orphan Products Development, Jan. 25, 1994.

42. We don't closely monitor the medical profession in terms of going beyond that specific use. We do monitor, however, manufacturers who would promote it for going beyond the approved or indicated use. ODA Hearing at 15 (statement of Dr. James S. Benson).

43. Id. at 8.

44. Unless the authority is delegated to the Commissioner, requiring the Secretary of Health and Human Services to withdraw the exclusivity would frankly add another delay to the process, thus permitting as much as possible of the original 7-year period to be effectively maintained. By contrast, FDA could act more quickly on its own.

45. Telephone conversation with Robert Steeves of FDA's Office of Orphan Products Development, January 25, 1994.

46. The idea of a patient cap was opposed in 1990 by Abbey Meyers of the National Organization for Rare Diseases on these grounds; ODA Hearing at 67.

47. See Anticompetitive Abuses at 146. If true, this would explain the reported four-year limit on exclusivity in the bill to be introduced this year; four years' sales at \$50 million accounts for \$200 million in cumulative sales. It would also equalize the definition of blockbuster drugs across FDA's jurisdiction. Circumstantial

evidence for this theory is provided by the fact that Senator Metzenbaum, who presided over the Anticompetitive Abuses hearing, will reportedly cosponsor the new bill.

48. Patricia J. Kenney, The Orphan Drug Act – Is it a Barrier to Innovation? Does it Create Unintended Windfalls?, 43 FOOD DRUG COSM. L. J. 667 (1988).

49. A lack of uniformity in drug firm accounting practices, complexities in properly allocating sales of a product approved for more than one disease, and difficulties in separating domestic and foreign research and sales are several factors that will lead to great difficulty in data collection. ... FDA has no experience in this area. Hence in our view, a sales cap provision is both bad policy and unadministrable. Testimony of Commissioner David A. Kessler, March 3, 1992, on 5. 2060 before the Senate Labor and Human Resources Committee at 6.

50. 5. REP. NO. 102-358, 102d Cong., 2d Sess. (1992) at 3.

51. Stephen Duzan, CEO of Immunex and President of the Industrial Biotechnology Association, quoted in

FORTUNE, Aug. 12, 1991, in S. REP. NO. 102-358, 102d Cong., 2d Sess. (1992) at 10. Contra, Patricia J. Kenney, The Orphan Drug Act – Is it a Barrier to Innovation? Does it Create Unintended Windfalls?, 43 FOOD DRUG

COSM. L. J. 667, 668 (1988): Genentech, for example, spent over \$200 million developing the genetically-engineered tissue plasminogen activator, Activase®.

52. [I]t seems to me that as a company sells \$80 million or \$90 million worth of a drug in a year it will start to lower its price, so it doesn't go over that \$100 million, and that might serve to keep the prices low. ODA Hearing at 62 (statement of Abbey S. Meyers).

53. Letter from Direct Action for Treatment Access to Senate Judiciary Committee, Feb. 28, 1992, in S. REP. NO. 102-358, 102d Cong., 2d Sess. (1992) (minority views) at 18.

54. A drug for instance, cystic fibrosis, might be very expensive, but it might save the children from repeated hospitalizations and save tens of thousands of dollars a year per patient. So there has to be a way to define what is reasonable. ODA Hearing at 60 (statement of Abbey S. Meyers).

55. Testimony, supra note 49, at 5.

56. Change the Orphan Products Board because it is ineffective and we really need a central office for rare diseases, and at the Assistant Secretary's level, to handle the problems. ODA Hearing at 62 (statement of Abbey S. Meyers).

57. See, e.g. Stephen E. Lawton, Controversy Under the Orphan Drug Act: Is Resolution on the Horizon?, 46 FOOD DRUG COSM. L. J. 327, 343. One senior Bush Administration HHS official strongly disputes this view, maintaining that HHS simply believed that the Act was not broken and therefore shouldn't be fixed. The official analogized the Department's views to the Hippocratic Oath: First, do no harm. Arguing that a veto was planned in advance, the official pointed to Secretary Sullivan's letter to Representative Waxman of June 20, 1990 and noted that the provisions

on shared exclusivity and retroactivity were the motivating factors for the veto. Further, the Department was extremely suspicious of the competing claims of the various parties and felt there was no way to be certain that the proposed solution was not worse. Author's conversation with senior Administration official, January 12, 1994.

58. The Secretary would be required to make the appointments in consultation with the Office and the Commissioner of FDA. This language is carefully written to avoid any Constitutional problems; in practice, however, it would be difficult for the Secretary to override the recommendations of the Office and FDA.

59. Arguably, the case of pentamidine reinforces the point. The Federal Government (the Center for Disease

Control) asked Lyphomed to undertake manufacture of pentamidine after a fire destroyed the only other supply.

Lyphomed received the seven-year provision for exclusivity; it is easy to imagine that one factor delaying the

approval of aerosolized pentamidine was that the Government felt bound by its earlier promise to Lyphomed, which it obtained in exchange for the research.

60. Telephone conversation with Robert Steeves, FDA Office of Orphan Products Development, January 25, 1994.

61. H.R. 1588, 103d Cong., 1st Sess. (1993), H.R. 1713, 102nd Cong., 1st Sess. (1991). Reportedly, Stark was most angered by the case of Amgen's drug Epogen for renal disease; Amgen had made \$400 million nearly pure profit from Epogen®. See 17 CORPORATE FINANCING WEEK No. 42, p.3. Most of this is paid from Medicare under its coverage for end-stage renal disease, and Medicare had not driven a good bargain. While the official retail price of Epogen® was 40c per 1000 units, Medicare paid \$11. BNA DAILY REPORT FOR EXECUTIVES, Oct. 15, 1991, at G3. Stark was also concerned about Genzyme's profits from Ceredase®, particularly since Federal funds had underwritten much of the development costs of the drug. See 139 CONG. REC. H1883 (daily ed., April 5, 1993) (statement of Rep. Stark).

62. The 1991 bill applied only once a company had recouped twice its development costs.

63. Even with refundability, the tax would also place a high ... administrative burden on companies to account precisely for development costs.

See Li-Hsien Rin-Laures and Diane Janofsky, Note, Recent Developments Concerning the Orphan Drug Act, 4 HARV. J. LAW AND TEC. 269, 284 (1991).

64. ODA Hearing at 46 (statement of Jean McGuire) McGuire.

65. Cumulative List of Orphan Product Designations and Approvals [Through December 31, 1993] (on file with FDA Office of Orphan Products Development). The two designations which have received marketing approval are both held by one company, but there is no guarantee it would win approval for the other four even if it decided to apply.

66. Id.

67. ODA Hearing at 16 (statement of Dr. James S. Benson) However, FDA cannot tell the sponsor exactly what population they will study. Id. at 23 (statement of Dr. Marlene E. Haffner).

68. Letter from Marlene E. Haffner, M.D., FDA Office of Orphan Products Development, to Jean F. McGuire and Jeffrey Levi, Nov. 30, 1989.

69. 21 CFR §316.3(3) (1993).

70. Telephone conversation with Robert Steeves, FDA Office of Orphan Products Development, January 25, 1994.

71. See 57 FED. REG. 62079 (Dec. 29, 1992).

72. An innovation that permits home use of a drug may not provide a major improvement in patient care if the patient will not maintain the regimen, or relies on regular professional visits for other reasons. ... There appear to be few absolutes applicable to this area. The only situation that FDA has identified as potentially providing a major contribution to patient care without a clear showing of a gain in safety and/or effectiveness is the development of an oral dosage form where the first drug was available only in a parenteral dosage form.

Marlene E. Haffner, M.D., Orphan Drugs: Where Have We Been Since AZT?, unpublished speech, May 28, 1992, at 14.

73. See, e.g., Abbey S. Meyers, The Impact of Orphan Drug Regulation on Patients and Availa
47 FOOD DRUG COSM. L. J. 9, 11 (1992). It may be said with some authority
that the Act's authors did not intend to create monopolies through exclusivity.
The authors intended to stop generic competition for seven years.

74. See 57 FED. REG. 62077 (Dec. 29, 1992). See also Letter from Thomas Wiggans of Serono to Rep. Waxman, March 2, 1990: The developer of a true orphan drug could not rely on the incentives of the Act if exclusivity could be easily lost just by changing the indication slightly. See id. at 12 for Meyers' response.

75. F-D-C REPORTS, THE PINK SHEET, T&G-8, June 15, 1992. The proposal was never offered as a formal amendment, perhaps because 5. 2060 never reached floor debate.

76. F-D-C REPORTS, THE PINK SHEET, T&G-9-10, Aug. 17, 1992.

77. 5. REP. NO. 102-358, 102d Cong., 2d Sess. (1992) at 2. Moving testimony about weaknesses in some of the programs was offered in Anticompetitive Abuses at 50ff.

78. Cf. National Childhood Vaccine Injury Act of 1986, 100 Stat. 3743, 3755. Information from conversation

with Robert Steeves, January 25, 1994. FDA has not taken a position on this proposal.

For a discussion of issues relating to liability for orphan drugs, see Li-Hsien Rin-Laures and Diane Janofsky, Note, Recent Developments Concerning the Orphan Drug Act, 4 HARV. J. LAW AND TEC. 269, 296 (1991).

79. See, e.g., ODA Hearing at 30 (statement of Abbey S. Meyers): we would be willing for you to take AIDS out of the Orphan Drug Act. See also id. at 38 (statement of Jean McGuire): specifically, we are recommending the immediate cessation of orphan designation for any HIV antivirals or for any drugs which are likely to be used consistently in combination with the antivirals or for those drugs that are meant for prophylaxis or treatment of certain conditions that are likely to threaten the majority of those individuals living with HIV.

80. The drug Immuno-C for treatment of cryptosporidiosis in AIDS patients recently received orphan designation. See AIDS WEEKLY, Nov. 15, 1993. One prominent advocate believes that there wouldn't be drugs to treat AIDS without the Orphan Drug Act. AZT was an old drug on a shelf for 25 to 30 years, had no patent on it. There was no reason for Burroghs-Wellcome to take it off the shelf without the 7 years exclusivity. ODA Hearing at 68 (statement of Abbey S. Meyers).

81. Until about 1989, an indication 'for the treatment of AIDS' was considered an acceptable indication Letter Marlene E. Haffner, M.D., FDA Office of Orphan Product Development, to Jean F. McGuire and Jeffrey Levi, Nov. 2, 1989.

82. [A] total of 1,341 cases of AIDS had been reported to CDC when President Reagan signed the Orphan Drug Act. ... The majority of early products being studied for AIDS and AIDS related conditions were designated orphan products. See Haffner, supra note 72 at 2.

83. ODA Hearing at 34 (statement of Abbey S. Meyers).

84. Id. at 33.

85. Jess Hordess, Letter to NEW ENGLAND JOURNAL OF MEDICINE, Nov. 21, 1989. See also REPORT OF THE NATIONAL COMMISSION ON ORPHAN DISEASES, U.S. Department of Health and Human Services, February 1989, at 98.

86. [W]e would be wrong to ignore the misfortunes of those who suffer from diseases that affect only a few.

Patricia J. Kenney, The Orphan Drug Act – Is it a Barrier to Innovation? Does it Create Unintended Windfalls?, 43 FOOD DRUG COSM. L. J. 667, 668 (1988).

87. ODA Hearing at 198 (statement of George Rathman).

88. Id. at 117 (statement of John McLaughlin).

- 89. Testimony, *supra* note 49, at 5.
- 90. ODA Hearing at 32 (statement of Abbey S. Meyers).
- 91. Haffner, *supra* note 72, at 6.
- 92. ODA Hearing at 23 (statement of Dr. James S. Benson).
- 93. Id. at 28. See also *id.* at 35 (statement of Abbey S. Meyers):

According to the August 4, 1989 issues of the journal Science, the orphan drug Eldypryl® represents a cost savings in the U.S. of \$10,000,000 for every week Parkinson's patients remain functional enough to work. This sum is saved in taxes paid to the government, and the absence of need for disability payments to Parkinson's patients.

94. When the Orphan Drug Act was designed, we were fully aware that abuses might occur and we agreed with

Mr. Waxman that the benefits of the Act outweighed the risks of abuses.
Letter from Abbey S. Meyers to Sen.

Edward M. Kennedy, July 8, 1988.